Supplementary methods

Electrophoretic mobility shift assays (EMSA)

Complementary DNA oligonucleotides (25 bp) centered on variant rs174575 alleles were synthesized by Takara (Japan) and labelled with biotin at the 3' end (**Table S3**). EMSA was performed using an EMSA/Gel-Shift Kit (Beyotime, China) according to the manufacturer's instructions. Additionally, for the competitive binding assay, unlabelled probes were added to the reaction mixtures at a 10-fold or 100-fold excess compared to that of the labelled probes and incubated for 20 minutes prior to the addition of labelled probes.

Chromatin immunoprecipitation qPCR (ChIP-qPCR)

ChIP assays were performed by ChIP assay kit (Cat# 10086, Millipore, USA) according to the manufacturer's instructions. Genomic DNA was extracted from the fixed-chromatin cells and sheared by sonication. Next, an antibody against E2F1 (Abcam, ab179445) and a nonspecific rabbit IgG (Santa Cruz, as control) were respectively incubated with cross linked protein/DNA overnight for immunoprecipitation using protein A/G magnetic beads. The purification and collection of DNA fragments using the Dr.GenTLE Precipitation Carrier Kit (Takara, Japan). The purified DNA library was analyzed by qPCR. The primers used in ChIP-qPCR are shown in **Table S3**.

Dual-luciferase reporter assay

The luciferase reporter assay was performed by using the Dual-Luciferase Reporter Kit (Promega, USA) as per the manufacturer's recommendations. Cells were co-transfected with constructed luciferase vector containing either the rs174575[G] or rs174575[C] allele and the pRL-SV40 Renilla luciferase plasmid (Promega, USA). For each sample, luciferase activity was determined by normalizing the luminescence value of Renilla luciferase to that of firefly luciferase.

Chromosome conformation capture (3C) assays

3C assays were performed as previously described (1) in CRC cell lines carrying different genotypes of SNP rs174575. Cells were fixed with 2% formaldehyde for 10 min and stopped with glycine for 5 minutes. Next, cells were lysed in lysis buffer and digested with NcoI enzyme (New England Biolabs) at 37°C overnight and T4 ligase ligation (Thermo Fisher) at 16°C for 4 hours. The cross-linked DNA fragments were extracted with phenol/chloroform and precipitated with ethanol. Bacterial artificial chromosome clones (BAC, RP11-5F17 and RP11-467L20, Thermo Fisher) covering the genome segment of the target regions, which were used to eliminate amplification efficiency differences among primers, were treated with the same procedure. Additionally, *GAPDH* was used to normalize cell background differences. Physical interactions among anchor and test primers were measured by qPCR. All 3C-qPCR primers (**Table S3**) were synthesized by TSINGKE Biological technology (Wuhan, China).

Cell proliferation assays

Cells were seeded and transfected in 24 well plates (5×10^4 cells per well). After 24 hours, cells were harvested by trypsin digestion and subsequently seeded in 96-well flat-bottomed plates, with each well containing 2,500 cells in 100 μl of cell suspension. After a specific time in culture, cell viability was measured using CCK-8 assays (Dojindo, Japan).

Colony formation assays

Cells were seeded into 6-well cell culture plates at a density of 2,000 cells per well. After 10 days, cells were washed twice with cold PBS, fixed with 3.7% formaldehyde and stained with crystal violet. The colony number in each well was counted.

Quantitative reverse transcription PCR (qRT-PCR)

Total RNA of cells or patients' tissues was extracted with TRIzol reagent (Thermo Fisher, USA). Reverse transcription was performed using the SuperScript®III First-Strand Synthesis System (Invitrogen, USA) and qPCR was performed with Power SYBRTM Green PCR Master Mix (Applied Biosystems, USA). Gene expression was normalized to that of *GAPDH,* which was used as an internal control. All primers used in qPCR are listed in **Table S3**.

eQTL analysis in our own CRC tissues

A total of 81 CRC patients were recruited from Tongji Hospital of Huazhong University of Science and Technology (HUST), Wuhan, China, and their demographic characteristics, are shown in **Table S4**. Genomic DNA used for SNP rs174575 genotyping was extracted from peripheral blood samples using the Relax Gene Blood DNA System Kit (Tiangen, China). The SNP rs174575 was genotyped by the TaqMan SNP real-time polymerase chain reaction (PCR) assay (Applied Biosystems, USA). The expression of candidate genes *FADS2* and *AP002754.2* were measured using qRT-PCR from tumor tissues of CRC patients. The *P* values were calculated by a two-sided Student's *t*-test. Informed consent was obtained from each subject, and this study was approved by the Institutional Review Board of Tongji Medical College, HUST.

Prostaglandin E2 (PGE2) measurement

Cell culture medium was collected and frozen at -80 °C until analysis. The levels of PGE2 released into the culture medium were determined by an enzyme linked immunosorbent assay (ELISA) kit (Cat# 500141, Cayman, USA) according to the manufacturer's protocol.

The serum levels of PGE2 in 81 CRC patients, which were recruited from Tongji Hospital of HUST, Wuhan, China, were measured by the ELISA kit (Cat# KGE004B, R&D Systems, USA) according to the manufacturer's protocol. The collection of serum was using a serum separator

tube and then it was centrifuged for 15 minutes at 1000 ×g at 4°C within 30 minutes of collection. To inhibit prostaglandin synthesis by COX-2, the indomethacin (Sigma-Aldrich, Germany) was added to serum collection tubes at a final concentration of approximately 10 μg/mL. Sample immediately was store -80°C until analysis and without repeated freeze-thaw cycles. We determined plasma PGE2 levels in triplicate samples from each person and the data presented for each person is an average of triplicate detections.

References:

1. Hagege H, Klous P, Braem C, Splinter E, Dekker J, Cathala G, et al. Quantitative analysis of chromosome conformation capture assays (3C-qPCR). Nature protocols. 2007;2:1722-33.

Supplementary figures

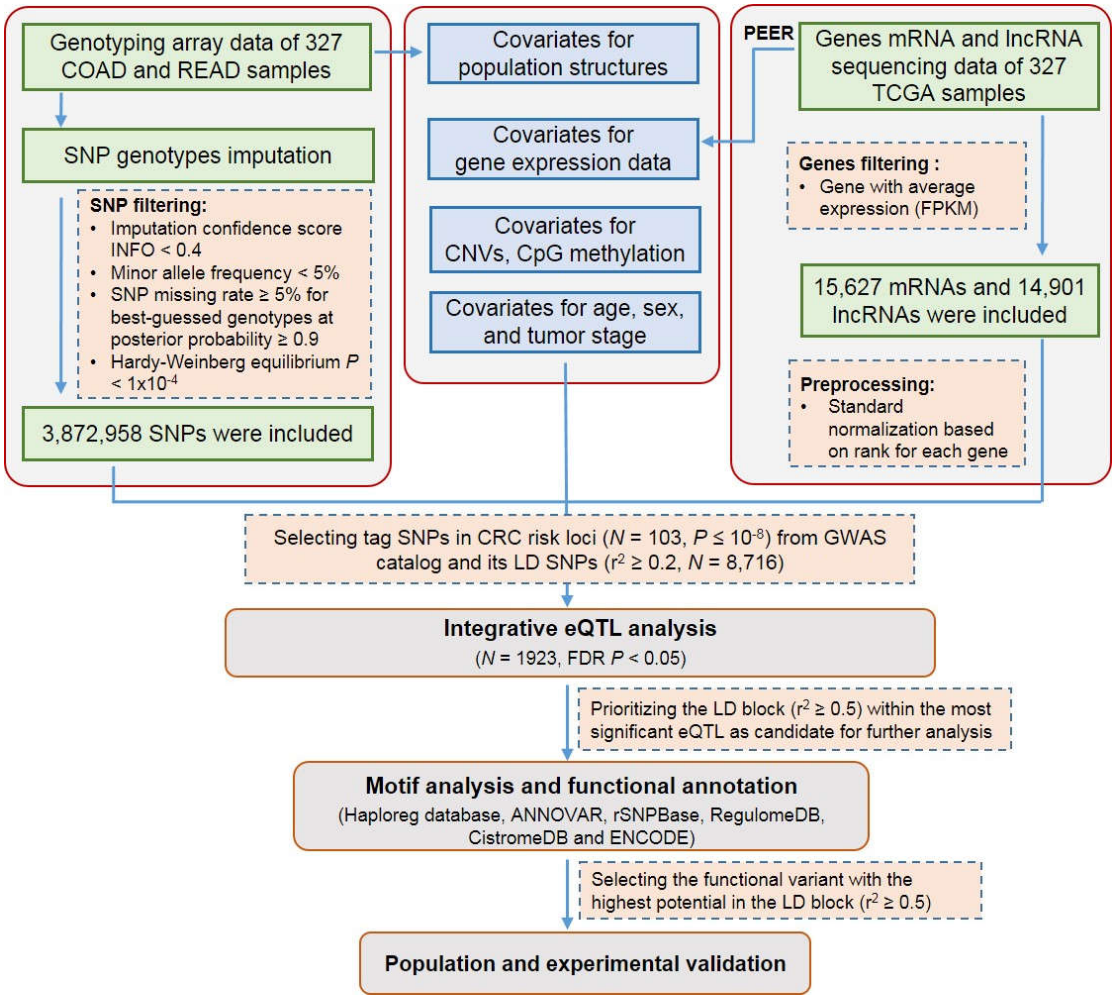

Figure S1. The flowchart of the integrative eQTL analyses

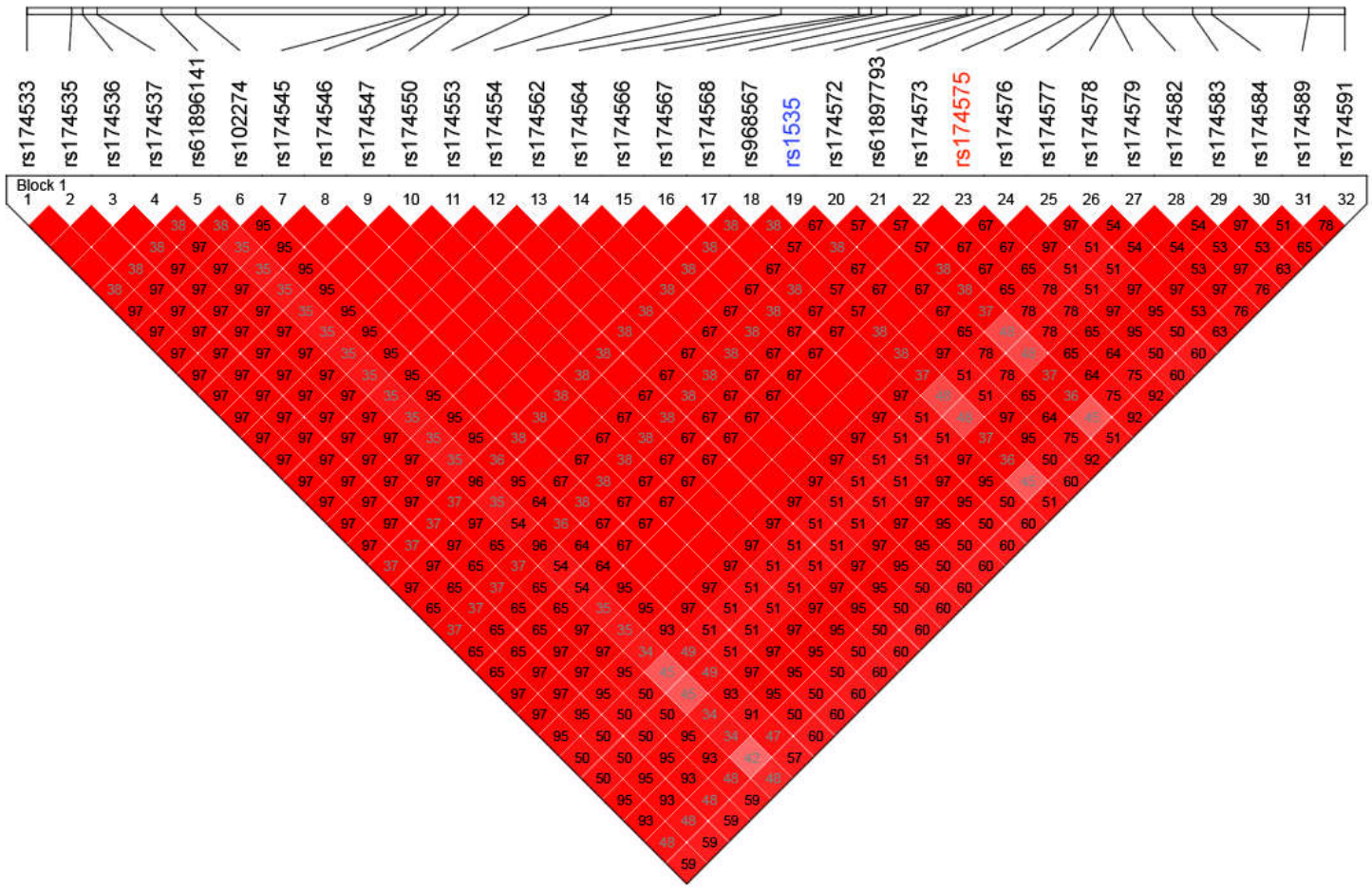

Figure S2. LD block plot ($r^2 \geq 0.5$) showing the r^2 value of candidate variants. The r^2 value between variants was estimated using the 1000 Genomes June 2014 EUR samples. We selected one most potentially functional variant in this block for further population and experimental validation and labeled it in red. The variant rs1535 (labeled in blue) is the tag SNP in this region identified by previous GWAS study.

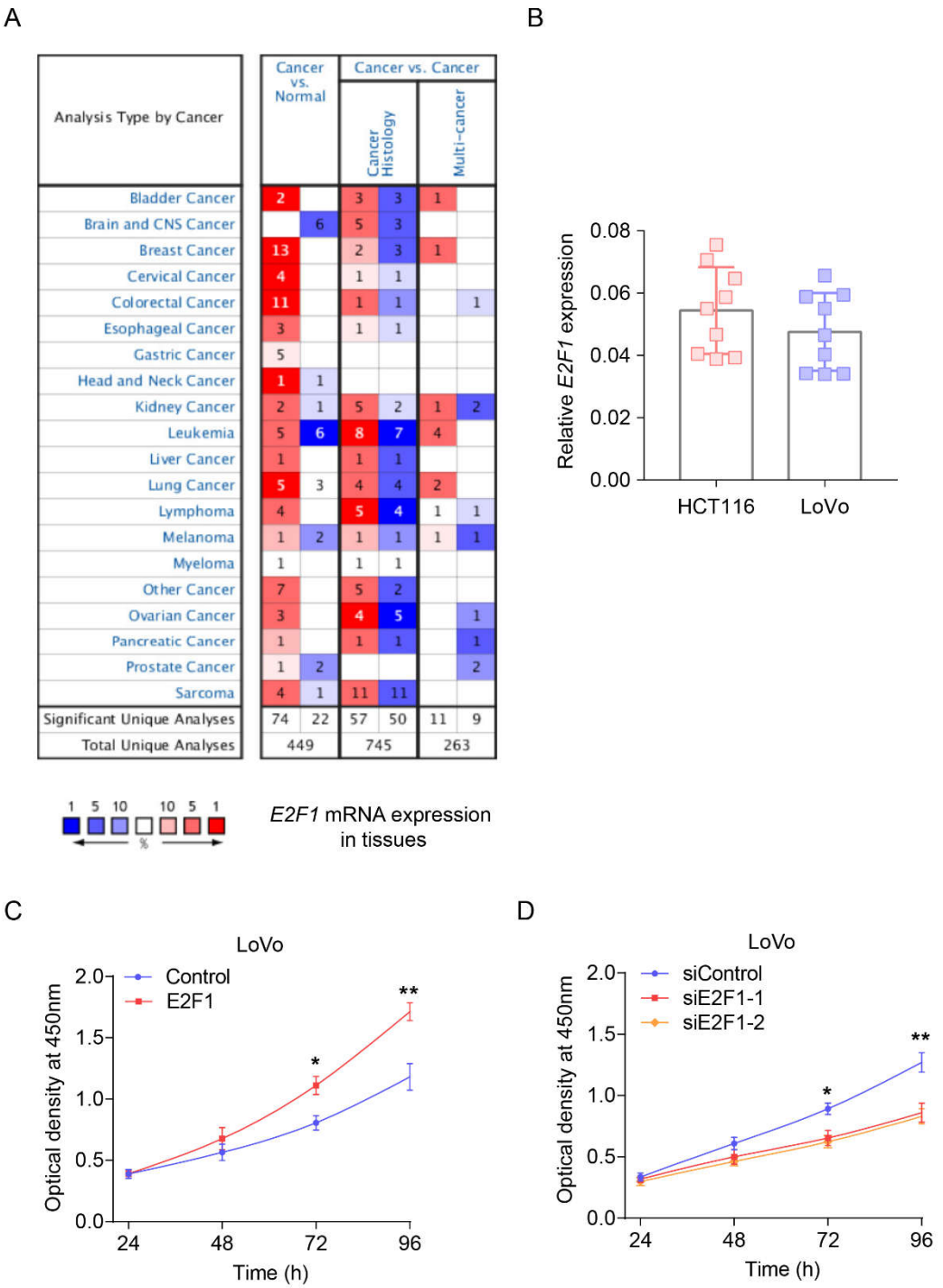

Figure S3. *E2F1* acts as a potential oncogene in CRC. A. *E2F1* expression levels were evaluated in multiple tumor tissues from the Oncomine database (https://www.oncomine.org). **B.** The baseline expression of *E2F1* in both HCT116 and LoVo cell lines. Data were shown as the means ± SD from three experiments, each with triplicates. Gene expression was normalized to that of *GAPDH*. **C, D.** The effect of *E2F1* overexpression or knockdown on cell proliferation in LoVo cells. Results were shown as the means ± s.e.m. from three experiments, each with six replicates. All $^{*}P < 0.05$, $^{**}P < 0.01$, compared with controls by a two-sided Student's *t*-test.

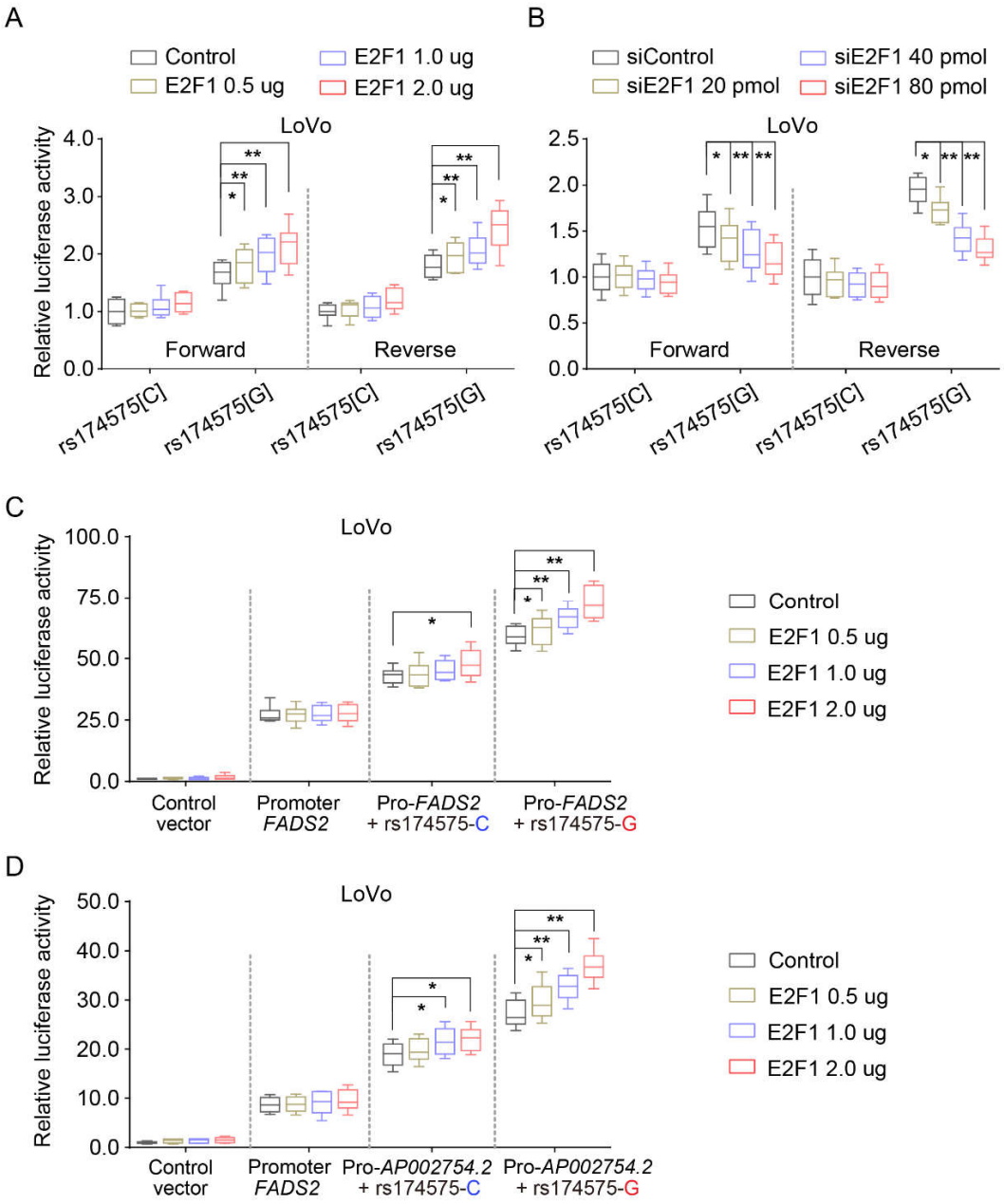

Figure S4. The effect of E2F1 on transcriptional activity of *FADS2* and *AP002754.2*. A, B. The effect of *E2F1* overexpression (A) or *E2F1* knockdown (B) on the relative luciferase activity of constructs containing the rs174575[C] or rs174575[G] allele in LoVo cells. **C, D.** The effect of *E2F1* overexpression (D) or *E2F1* knockdown (E) on allele-specific enhancer activity of variant rs174575 for *FADS2* and *AP002754.2* in LoVo cells. All experiments were performed in triplicate and each with three replicates. Data were presented as the median (minimum to maximum) and $^{**}P < 0.01$, $^{*}P < 0.05$ were calculated by a two-sided Student's *t*-test.

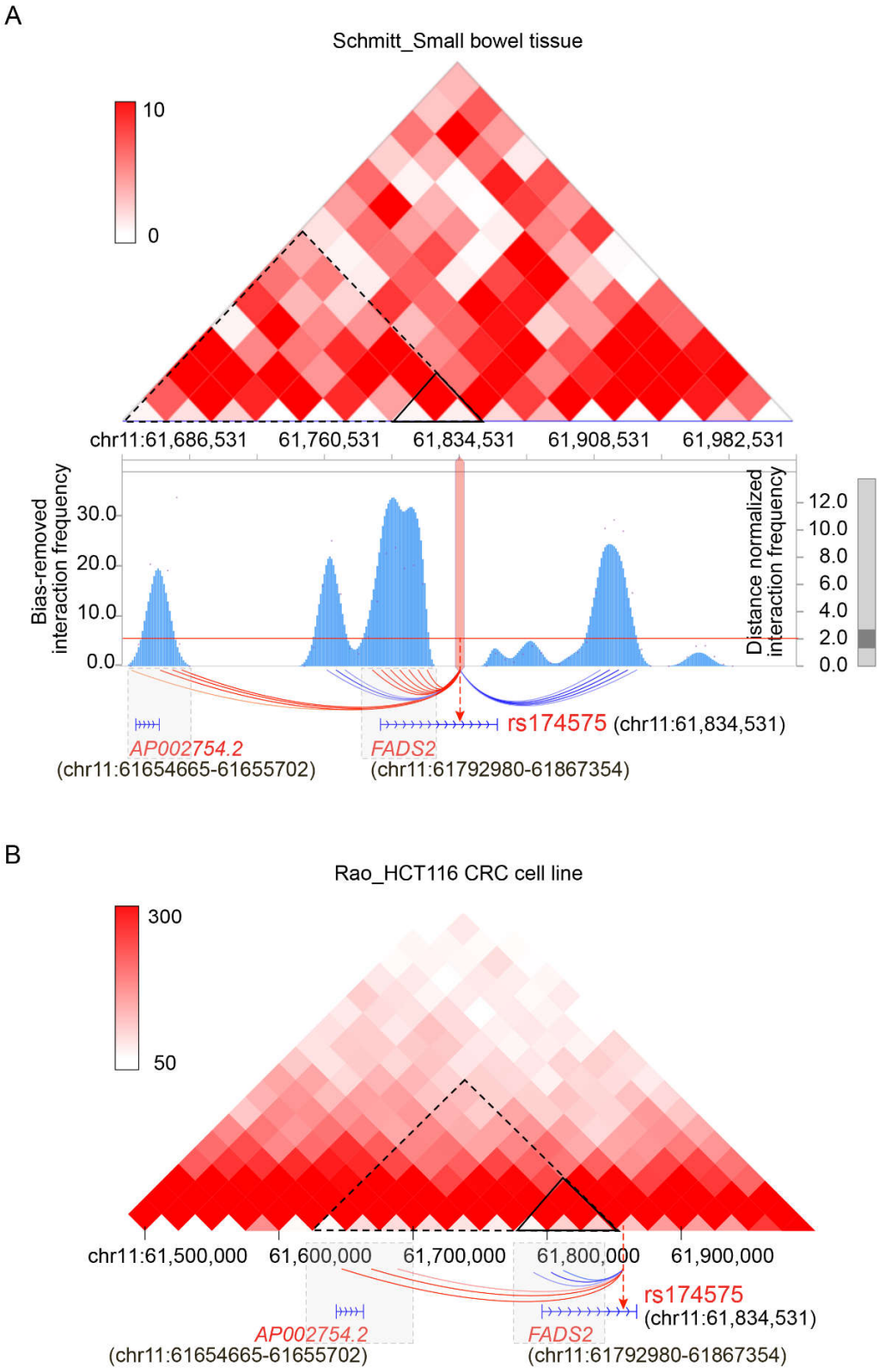

Figure S5. Long-Range chromatin looping formed between enhancer region containing risk SNP rs174575 and *FADS2* promoter or *AP002754.2* promoter. A, B. There have strong interactions between the region containing SNP rs174575 and *FADS2* promoter or *AP002754.2* promoter (the black triangle box) in the small bowel tissue (A) provided form 3D Genome browser (http://promoter.bx.psu.edu/hi-c/index.html) and HCT116 CRC cell line (B) provided from 3D interaction viewer and database (http://kobic.kr/3div/).

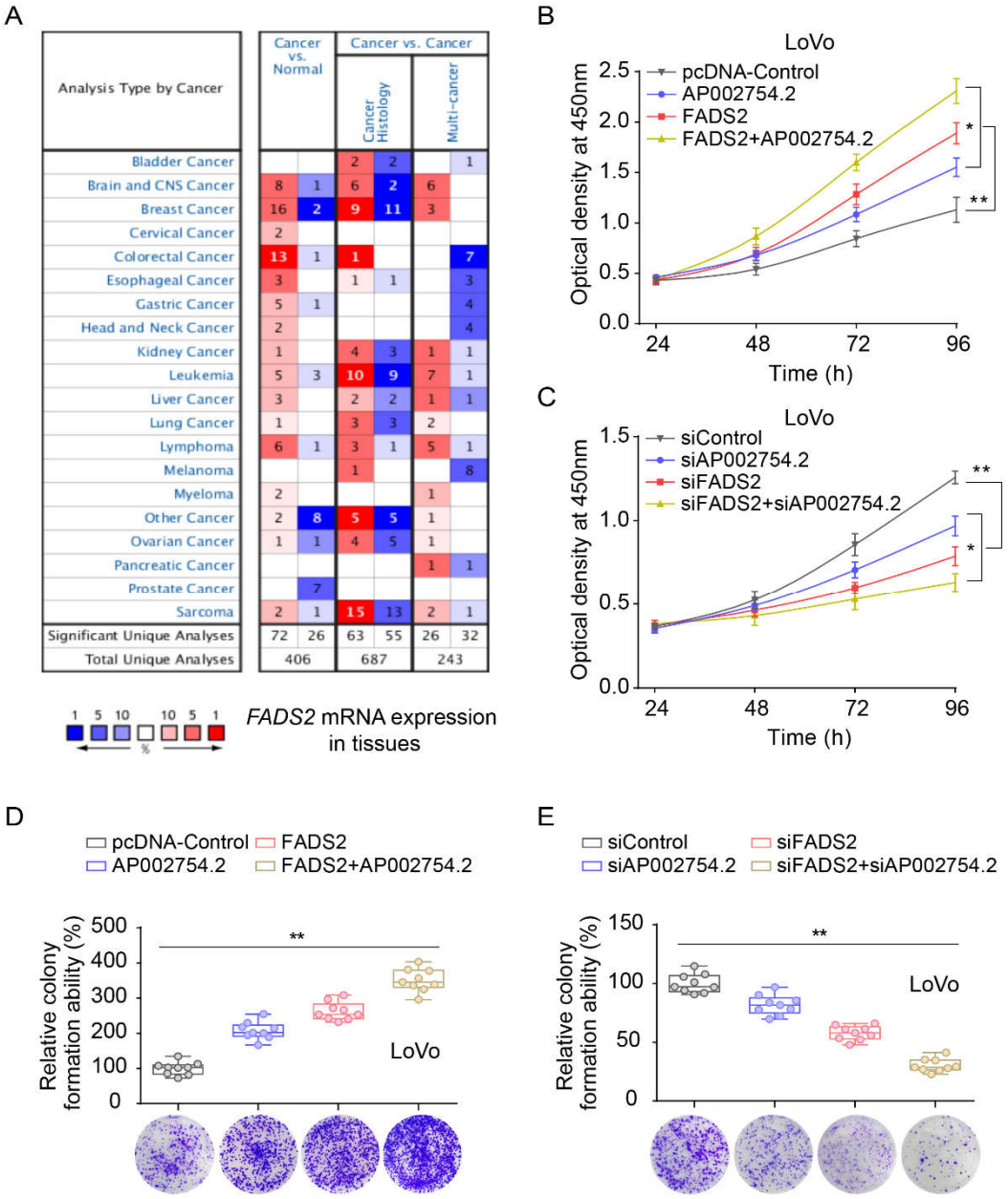

Figure S6. *FADS2* and *AP002754.2* functions as oncogenes provoking cell proliferation. **A.** *FADS2* expression levels were evaluated in multiple tumor tissue types from the Oncomine database (https://www.oncomine.org). **B, C.** The effect of *FADS2* and *AP002754.2* overexpression (B) or knockdown (C) on cell proliferation in LoVo cells. Results were shown as the means ± s.e.m. from three experiments, each with six replicates. All **P* < 0.05, ***P* < 0.01, compared with controls by a two-sided Student's *t*-test. **D, E.** The effect of *FADS2* and *AP002754.2* overexpression (D) or knockdown (E) on colony formation ability in LoVo cells. The results present colony formation ability relative to control cells (set to 100%); Data were shown as the median (minimum to maximum) from three experiments, each with three replicates. All ***P* < 0.01 were calculated by one-way ANOVA.

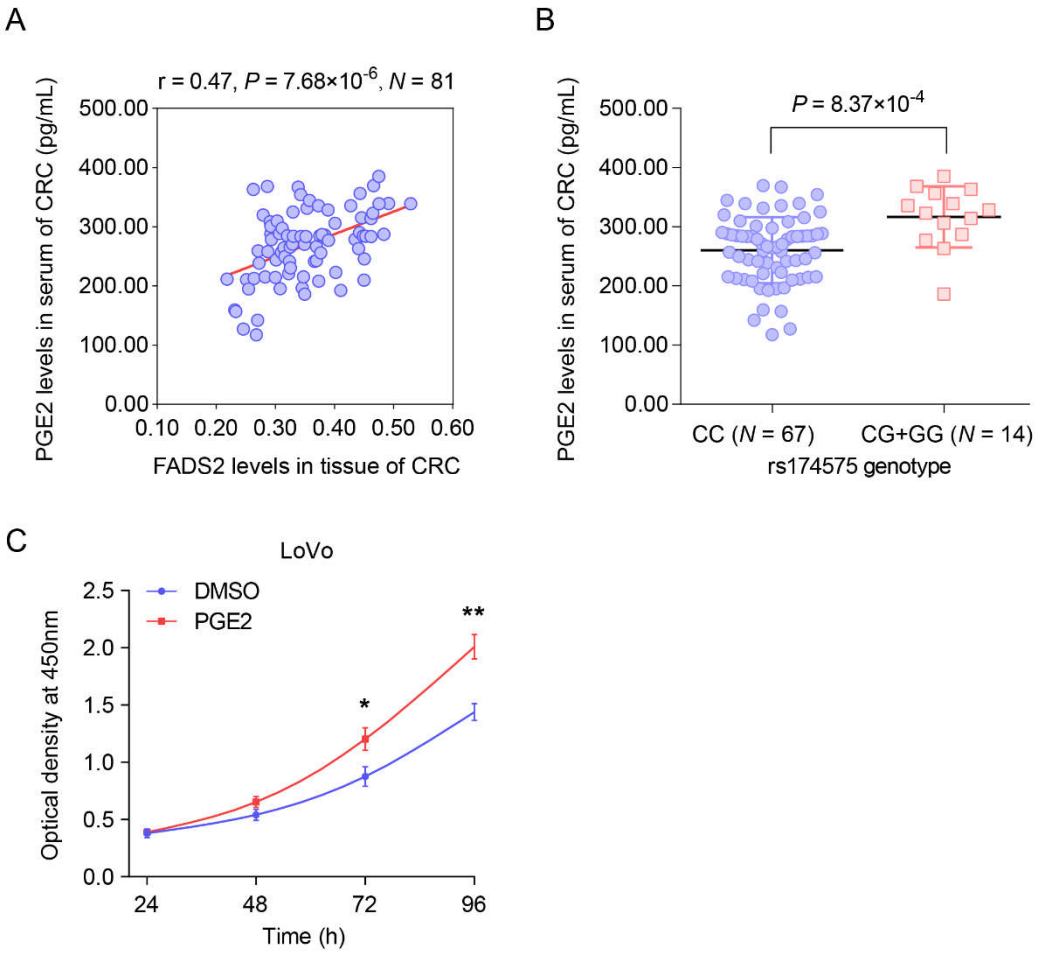

Figure S7. PGE2 is found to promote CRC cell proliferation. A. The correlation between FADS2 and PGE2 levels in serum of CRC patients. The *P* value and *r* value were calculated by Spearman's correlation analysis. **B.** The correlation of rs174575 genotype with PGE2 levels in the serum of CRC samples. Data were shown as the mean ± SD and *P* value was calculated using a two-sided Student's *t*-test. **C.** The effect of PGE2 (treatment for 24 hours at 10uM) on LoVo cell proliferation. Results were shown as the means ± s.e.m. from three experiments, each with six replicates. All $*P < 0.05$, $**P < 0.01$, compared with DMSO controls by a two-sided Student's *t*-test.

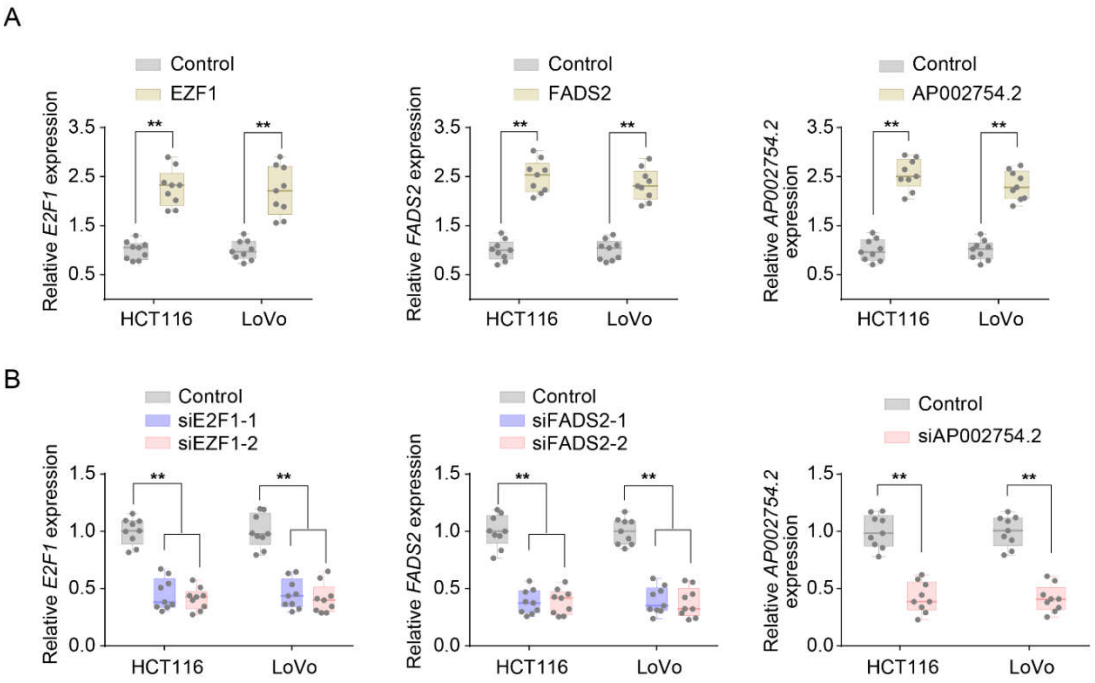

Figure S8. Determination of the transfection efficiency. A, B. Relative expression levels of *E2F1*, *FADS2* and *AP002754.2* overexpression (A) and knockdown (B) were determined by qRT–PCR method in CRC HCT116 and LoVo cell lines. Data were presented as the median (minimum to maximum) from three experiments, each with three replicates and all $^{**}P < 0.01$ were calculated by a two-sided Student's *t*-test.

Supplementary tables:

Table S1. Colorectal cancer risk signals associated at genome-wide significance ($P \leq$ 1.00E-08)

Lead variant	Locus	Chr	Position	Alleles‡	*P* value	Nearby gene
rs72647484	1p36.12	1	22261235	T/C	1.00E-08	5kb 5' of MIR4418
rs186507655	1p36.33	1	1351675	G/A	5.00E-10	1kb 3' of MXRA8
rs6687758	1q41	1	221991606	A/G	1.00E-08	6.6kb 3' of RP11-400N13.2
rs6691195	1q41	1	221989031	C/A	3.00E-10	4.1kb 3' of RP11-400N13.2
rs6691170	1q41	1	221872104	G/T	1.00E-09	8.9kb 3' of RP11-815M8.1
rs11903757	2q32.3	2	191722478	T/C	4.00E-08	34kb 3' of NABP1
rs992157	2q35	2	218290058	G/A	2.00E-09	PNKD
rs812481	3p14.1	3	66392011	C/G	2.00E-08	LRIG1
rs17659990	3p21.2	3	50713718	C/T	5.00E-09	DOCK3
rs35360328	3p22.1	3	40883471	T/A	6.00E-13	21kb 3' of RP11-761N21.1
rs481519	3p24.1	3	27285723	C/T	2.00E-09	NEK10
rs10936599	3q26.2	3	169774313	C/T	3.00E-08	MYNN
rs7679673	4q24	4	105140377	C/A	1.00E-10	AC004069.2
rs35509282	4q32.2	4	162412253	T/A	8.00E-09	248kb 5' of FSTL5
rs58791712	5p13.1	5	40281695	G/T	7.00E-14	12kb 3' of U1
rs2735940	5p15.33	5	1296371	A/G	3.00E-13	1.3kb 5' of TERT
rs7725218	5p15.33	5	1282299	G/A	2.00E-10	TERT
rs1862626	5q11.2	5	56737113	G/T	4.00E-12	34kb 5' of AC008940.1
rs254563	5q31.1	5	135104736	G/A	1.00E-09	CTC-203F4.1
rs647161	5q31.1	5	135163402	C/A	2.00E-14	CTC-203F4.1
rs4711689	6p21.1	6	41725074	G/A	4.00E-08	RP11-298J23.5
rs1321311	6p21.2	6	36655123	C/A	1.00E-10	PI16
rs7758229	6q25.3	6	160419220	G/T	8.00E-09	SLC22A3
rs16892766	8q23.3	8	116618444	A/C	4.00E-24	24kb 3' of EIF3H
rs2450115	8q23.3	8	116611854	T/C	1.00E-12	30kb 3' of EIF3H
rs6469656	8q23.3	8	116635549	G/A	2.00E-12	6.6kb 3' of EIF3H
rs2450115	8q23.3	8	116611854	T/C	1.24E-12	30kb 3' of EIF3H
rs6469656	8q23.3	8	116635549	G/A	2.03E-12	6.6kb 3' of EIF3H
rs140355816	8q23.3	8	116562277	C/G	2.00E-08	80kb 3' of EIF3H
rs76316943	8q24.11	8	116836068	G/A	2.00E-11	UTP23
rs6983267	8q24.21	8	127401060	G/T	8.00E-27	RP11-382A18.1
rs12682374	8q24.21	8	127398703	C/G	7.00E-29	RP11-382A18.1
rs10505477	8q24.21	8	127395198	A/G	3.00E-13	RP11-382A18.1
rs7014346	8q24.21	8	127412547	A/G	2.00E-08	RP11-382A18.1
rs9409565	9q22.32	9	94488752	C/T	2.00E-08	956bp 3' of RP11-533K9.2
rs11255841	10p14	10	8697617	T/A	3.00E-12	41kb 5' of RN5S299
rs9733843	10p14	10	8676041	A/G	1.00E-14	19kb 5' of RN5S299
rs10795668	10p14	10	8659256	G/A	5.00E-15	2.4kb 5' of RN5S299
rs4143094	10p14	10	8047173	T/G	9.00E-09	3.3kb 3' of RP11-379F12.7
rs704017	10q22.3	10	79059375	A/G	2.00E-08	RP11-202P11.1
rs1035209	10q24.2	10	99585609	C/T	1.00E-08	16kb 5' of snoU13
rs11190164	10q24.2	10	99591947	A/G	4.00E-08	9.8kb 5' of snoU13
rs4919687	10q24.32	10	102835491	G/A	8.00E-12	CYP17A1
rs11196172	10q25.2	10	112967084	G/A	4.00E-10	TCF7L2
rs12241008	10q25.2	10	112520943	T/C	3.00E-12	VTI1A
rs10506868	10q25.2	10	112559621	C/T	4.00E-09	VTI1A
rs11200014	10q26.13	10	121575416	G/A	8.00E-35	FGFR2

rs1535	11q12.2	11	61830500	A/G	4.00E-08	FADS2
rs174594	11q12.2	11	61852357	C/A	2.00E-13	FADS2
rs174537	11q12.2	11	61785208	G/T	9.00E-21	C11orf9
rs174550	11q12.2	11	61804006	T/C	7.00E-10	FADS1
rs7931342	11q13.3	11	69227030	T/G	4.00E-14	55kb 5' of RP11-554A11.8
rs3824999	11q13.4	11	74634505	T/G	4.00E-10	POLD3
rs148883465	11q22.3	11	103813371	A/G	3.00E-08	RP11-563P16.1
rs3802842	11q23.1	11	111300984	C/A	5.00E-19	C11orf93
rs6589219	11q23.1	11	111302186	G/C	2.00E-09	C11orf93
rs2965667	12p12.3	12	17291799	A/T	5.00E-09	218kb 3' of RP11-871F6.3
rs2238126	12p13.2	12	11856807	A/G	3.00E-11	ETV6
rs11064437	12p13.31	12	6872998	C/T	4.00E-11	SPSB2
rs10849432	12p13.31	12	6276561	C/T	4.00E-10	34kb 5' of PLEKHG6
rs3217810	12p13.32	12	4279105	C/T	2.00E-11	CCND2
rs4572213	12p13.32	12	4256383	A/T	2.00E-09	RP11-264F23.3
rs10774214	12p13.32	12	4259186	T/C	1.00E-10	RP11-264F23.3
rs4768903	12q13.12	12	50651666	A/G	4.00E-08	DIP2B
rs34245511	12q13.12	12	50179650	G/C	3.00E-08	LIMA1
rs11169552	12q13.12	12	50761880	C/T	2.00E-10	1.8kb 5' of ATF1
rs73110464	12q13.13	12	52918828	C/T	2.00E-15	KRT8
rs3184504	12q24.12	12	111446804	T/C	2.00E-10	SH2B3
rs73208120	12q24.22	12	117309785	T/G	3.00E-08	NOS1
rs11571833	13q13.1	13	32398489	A/T	8.00E-12	BRCA2
rs11571818	13q13.1	13	32394673	T/C	5.00E-10	BRCA2
rs56084662	13q13.1	13	32295727	G/A	4.00E-09	FRY
rs4444235	14q22.2	14	53944201	T/C	1.00E-09	4.2kb 3' of MIR5580
rs17094983	14q23.1	14	58722643	G/A	8.00E-10	49kb 3' of AL121819.1
rs11844632	14q24.1	14	68559662	G/A	3.00E-10	RAD51B
rs73376930	15q13.3	15	32720301	A/G	4.00E-18	GREM1
rs4779584	15q13.3	15	32702555	T/C	1.00E-08	5.5kb 3' of SCG5
rs2293582	15q13.3	15	32718211	G/A	3.00E-11	RP11-758N13.1
rs16973225	15q25.2	15	81937658	A/C	8.00E-09	16kb 3' of RP11-276M12.1
rs9929218	16q22.1	16	68787043	G/A	1.00E-08	CDH1
rs847208	16q24.1	16	86220445	C/A	3.00E-09	55kb 3' of Y_RNA
rs1078643	17p12	17	10803924	G/A	8.40E-13	RP11-963H4.6
rs12603526	17p13.3	17	897353	T/C	3.00E-08	NXN
rs12601991	17q12	17	37741642	G/T	1.00E-09	HNF1B
rs4939827	18q21.1	18	48927093	T/C	3.00E-30	SMAD7
rs7229639	18q21.1	18	48924606	A/G	3.00E-12	SMAD7
rs4939567	18q21.1	18	48925503	G/A	1.00E-22	SMAD7
rs7226855	18q21.1	18	48927678	A/G	4.00E-23	SMAD7
rs4808075	19p13.11	19	17279482	T/C	2.00E-09	128bp 3' of BABAM1
rs7252505	19q13.11	19	33084158	G/A	4.00E-08	GPATCH1
rs10411210	19q13.11	19	33041394	C/T	5.00E-09	RHPN2
rs1800469	19q13.2	19	41354391	A/G	1.00E-08	TMEM91
rs961253	20p12.3	20	6423634	C/A	6.00E-11	23kb 5' of RP11-199O14.1
rs4813802	20p12.3	20	6718948	T/G	1.00E-09	12kb 3' of RP5-859D4.3
rs2423279	20p12.3	20	7831703	T/C	3.00E-12	51kb 3' of HAO1
rs11907546	20q11.22	20	34131991	C/T	3.00E-09	20kb 5' of EIF2S2
rs2300206	20q11.22	20	34002002	G/C	2.00E-08	RALY
rs6065668	20q13.12	20	43904181	C/T	4.00E-11	8.7kb 3' of RP5-1030M6.3
rs6066825	20q13.13	20	48723580	A/G	4.00E-09	PREX1

rs964293	20q13.2	20	54200178	C/A	5.00E-09	7.7kb 5' of PFDN4
rs2427308	20q13.33	20	62394395	C/T	2.00E-13	CABLES2
rs6061231	20q13.33	20	62381861	C/A	8.00E-11	5.2kb 5' of RPS21
rs4925386	20q13.33	20	62345988	T/C	2.00E-10	LAMA5

Abberevation: Chr., Chromosome.

‡ Reference allele/Mutation allele.

Table S2. Summary of characteristics of individuals in the two stage case-control studies

	Discovery phase			Replication phase			Combined study		
	Cases *N* (%)	Controls *N* (%)	*P*†	Cases *N* (%)	Controls *N* (%)	*P*†	Cases *N* (%)	Controls *N* (%)	*P*†
Total	1,524	1,522		4,500	8,500		6,024	10,022	
Gender			0.498			0.041			0.037
Male	923 (60.56)	940 (61.76)		2,695 (61.73)	5,247 (59.89)		3,618 (60.06)	6,187 (61.73)	
Female	601 (39.44)	582 (38.24)		1,805 (38.27)	3,253 (40.11)		2,406 (39.94)	3,835 (38.27)	
Age (mean ± SD)	58.84±11.86	60.48±10.11	<0.001	61.34±11.66	59.64±12.03	<0.001	59.43±11.99	61.21±11.44	<0.001
Age group (year)			0.041			0.705			0.110
≤50	327 (21.46)	281 (18.46)		690 (15.33)	1,284 (15.11)		1,017 (16.88)	1,565 (15.62)	
51-60	420 (27.56)	433 (28.45)		1,233 (27.40)	2,273 (26.74)		1,653 (27.44)	2,706 (27.00)	
61-70	484 (31.76)	542 (35.61)		1,516 (33.69)	2,869 (33.75)		2,000 (33.20)	3,411 (34.04)	
≥71	293 (19.23)	266 (17.48)		1,061 (23.58)	2,074 (24.40)		1,354 (22.48)	2,340 (23.35)	
Smoking status			<0.001			0.037			0.003
No	1042 (68.37)	1197 (78.65)		2,721 (60.47)	5,299 (62.34)		3,763 (62.47)	6,496 (64.82)	
Yes	482 (31.63)	325 (21.35)		1,779 (39.53)	3,201 (37.66)		2,261 (37.53)	3,526 (35.18)	
Drinking status			0.725			0.145			0.080
No	1133 (74.34)	1123 (73.78)		3,276 (72.80)	6,084 (71.58)		4,409 (73.19)	7,477 (71.91)	
Yes	391 (25.66)	399 (26.22)		1,224 (27.20)	2,416 (28.42)		1,615 (26.81)	2,911 (28.09)	

SD, standard deviation.

†All *P* values were calculated by a two sided Student's *t* test for age or the Pearson's χ^2 test for gender, age group, smoking status, and drinking status.

Table S3. Probes or primers sequence used in the study

Electrophoretic mobility shift assay (5'-3')		
rs7959129-C	Forward	GAAATGGCTGAGCAGCAACCAAGGT
	Reverse	ACCTTGGTTGCTGCTCAGCCATTTC
rs7959129-G	Forward	GAAATGGCTGAGGAGCAACCAAGGT
	Reverse	ACCTTGGTTGCTCCTCAGCCATTTC
qRT-PCR (5'-3')		
GAPDH	Forward	CCTCCCGCTTCGCTCTCT
	Reverse	TGGCGACGCAAAAGAAGAT
E2F1	Forward	GACGGCTTGAGGGGTTGAC
	Reverse	TGCAGGGTCTGCAATGCTAC
FADS2	Forward	GTCATCGGGCACTACGCTG
	Reverse	ACCAATCAGCAGGGGTTTCA
AP002754.2	Forward	GGCTTCCTGCTATCCTACCCT
	Reverse	TTATTGGTCTGTTGCTGCCTG
Chromosome conformation capture (3C) assay (5'-3')		
E1-P1~P17	Forward	CCCCACCACCCCCATTGCCTCTG
E1-P1	Reverse	CACCCATCCCACTCCCAACCACC
E1-P2	Reverse	GGAATCTCTGAGCGCCTGAACCA
E1-P3	Reverse	AGCCCTGGATCTTGACCCCCTTT
E1-P4	Reverse	ATTTATTGAGCTTCCAATTACGG
E1-P5	Reverse	GGGCTTTGGAAGGCGGCTGAACG
E1-P6	Reverse	GGGTTTTAGTTGGAAGTAGCAAA
E1-P7	Reverse	ATGGTGTCCTTTTTGTTGTGTGG
E1-P8	Reverse	TGGTTTTCATGCGCTGTTTTTGT
E1-P9	Reverse	AGAAATGAGTTTAAAAGTAAAGAG
E1-P10	Reverse	TCTGAGCTTCCACGCTTTCCCCT
E1-P11	Reverse	CATCCACCTCAGCCTCCCGAAGT
E1-P12	Reverse	CCTCTGACACTTCATCCATCCCT
E1-P13	Reverse	CCTTTGTTTTGCTTGGAATTTGG
E1-P14	Reverse	GCTCCTCCCACGCTTGGCCATCA
E1-P15	Reverse	CTGCTGTCCACCAAACCTTCTCC
E1-P16	Reverse	CTCTGCACTGGTTGTTAAATATT
E1-P17	Reverse	TATTCCTTCCATACTTTGTTTAA
GAPDH	Forward	ACAGTCCATGCCATCACTGCC
GAPDH	Reverse	GCCTGCTTCACCACCTTCTTG
Chromatin immunoprecipitation qPCR (ChIP-qPCR) assay (5'-3')		
DNA fragment spanning rs174575	Forward	ACATGAGCAACACTCCTGGC
	Reverse	CCCTGCCTTGACCTTGGTT
DNA fragment of *FADS2* promoter	Forward	CCCCAAGAGGCTGTGCG
	Reverse	TAAGCTCGCTCTCCCTTCTCA
DNA fragment of *AP002754.2* promoter	Forward	GACACTTCCCCATGGAAGCA
	Reverse	TGCCAAGAACATTAACCAGGC

siRNAs		
	siRNA1	CCTGATGAATATCTGTACT
siE2F1	siRNA2	TGGACCACCTGATGAATAT
	siRNA3	CAGAGCAGATGGTTATGGT
	siRNA1	GAACCACCTTGTCCACAAA
siFADS2	siRNA2	TGACCATGATCGTCCATAA
	siRNA3	GGACGCCTACCTTCACAAA
siAP002754.2	Smart Silencer	GCAGCAACAGACCAATAAA CTGCTATCCTACCCTTGAA GACCAATAAAGGCTTCCAA GGCTTCCTGCTATCCTACCC AAGCTGGCTTCCTGCTATCC TAACTGCCAGGCAGCAACAG

Table S4. Characteristics of patients with CRC tissues in this study

Sample_ID	Sex	Age (year)	Drinking status	Smoking status	TNM stage
CRC_1	Male	77	Drinker	Smoker	T3N2Mx
CRC_2	Female	60	Drinker	Nonsmoker	T4N0Mx
CRC_3	Male	58	Drinker	Nonsmoker	T3N1Mx
CRC_4	Male	68	Nondrinker	Nonsmoker	T4N0Mx
CRC_5	Male	76	Drinker	Smoker	T2N0Mx
CRC_6	Male	74	Drinker	Nonsmoker	T3N0Mx
CRC_7	Female	78	Drinker	Smoker	T3N0Mx
CRC_8	Male	85	Drinker	Nonsmoker	T3N0Mx
CRC_9	Female	33	Drinker	Smoker	T3N1Mx
CRC_10	Female	51	Drinker	Smoker	T3N1Mx
CRC_11	Male	57	Drinker	Smoker	T3N1Mx
CRC_12	Male	66	Drinker	Smoker	T4N0M0
CRC_13	Male	82	Drinker	Smoker	T3N1Mx
CRC_14	Male	53	Nondrinker	Nonsmoker	T4N0Mx
CRC_15	Male	65	Drinker	Smoker	T2N0Mx
CRC_16	Male	55	Nondrinker	Nonsmoker	T3N2Mx
CRC_17	Male	65	Nondrinker	Nonsmoker	T3N1Mx
CRC_18	Male	68	Drinker	Nonsmoker	T4N0Mx
CRC_19	Male	46	Drinker	Nonsmoker	T4N2Mx
CRC_20	Female	75	Drinker	Smoker	T4N0Mx
CRC_21	Male	65	Drinker	Smoker	T3N1Mx
CRC_22	Female	56	Drinker	Smoker	T3N0Mx
CRC_23	Male	52	Drinker	Nonsmoker	T3N0Mx
CRC_24	Male	50	Drinker	Nonsmoker	T3N0Mx
CRC_25	Female	64	Drinker	Smoker	T2N0Mx
CRC_26	Male	62	Drinker	Smoker	T3N0Mx
CRC_27	Female	77	Drinker	Smoker	T2N0Mx
CRC_28	Female	51	Drinker	Smoker	T4N2Mx
CRC_29	Male	66	Drinker	Smoker	T3N0Mx
CRC_30	Male	63	Drinker	Smoker	T3N0Mx
CRC_31	Male	51	Drinker	Smoker	T3N2Mx
CRC_32	Female	65	Drinker	Smoker	T4N1Mx
CRC_33	Male	70	Drinker	Smoker	T3N1Mx
CRC_34	Female	77	Drinker	Smoker	T3N0Mx
CRC_35	Female	79	Drinker	Smoker	T4N1Mx
CRC_36	Male	50	Drinker	Smoker	T4N0Mx
CRC_37	Male	84	Drinker	Nonsmoker	T3N0Mx
CRC_38	Female	57	Drinker	Smoker	T3N1Mx
CRC_39	Female	56	Drinker	Smoker	T3N0Mx
CRC_40	Male	41	Drinker	Nonsmoker	T4N2Mx
CRC_41	Female	80	Drinker	Smoker	T3N0Mx
CRC_42	Female	85	Drinker	Smoker	T3N0Mx
CRC_43	Female	63	Drinker	Smoker	T4N1M1
CRC_44	Male	57	Drinker	Nonsmoker	T3N0Mx
CRC_45	Male	87	Drinker	Smoker	T3N2Mx
CRC_46	Male	71	Nondrinker	Nonsmoker	T2N0Mx
CRC_47	Male	57	Nondrinker	Nonsmoker	T3N0Mx
CRC_48	Male	56	Nondrinker	Smoker	T3N1Mx
CRC_49	Female	61	Drinker	Smoker	T3N0Mx
CRC_50	Male	70	Nondrinker	Nonsmoker	T3N2Mx

CRC_51	Male	69	Drinker	Smoker	T2N0Mx
CRC_52	Male	43	Drinker	Nonsmoker	T3N0Mx
CRC_53	Male	64	Nondrinker	Nonsmoker	T3N0Mx
CRC_54	Male	65	Drinker	Smoker	T4N1Mx
CRC_55	Male	78	Nondrinker	Nonsmoker	T3N0Mx
CRC_56	Male	74	Nondrinker	Nonsmoker	T4N2Mx
CRC_57	Male	50	Drinker	Nonsmoker	T4N2Mx
CRC_58	Female	71	Drinker	Smoker	T3N1Mx
CRC_59	Male	72	Drinker	Smoker	T3N1Mx
CRC_60	Female	38	Drinker	Smoker	T3N0Mx
CRC_61	Female	74	Drinker	Smoker	T3N0Mx
CRC_62	Male	85	Drinker	Smoker	T3N0Mx
CRC_63	Male	63	Drinker	Smoker	T4N0Mx
CRC_64	Female	54	Drinker	Smoker	T4N1Mx
CRC_65	Female	56	Drinker	Smoker	T3N2Mx
CRC_66	Female	64	Drinker	Smoker	T3N0Mx
CRC_67	Male	53	Drinker	Smoker	T3N0Mx
CRC_68	Female	61	Drinker	Smoker	T3N0Mx
CRC_69	Male	82	Drinker	Nonsmoker	T4N2Mx
CRC_70	Female	58	Drinker	Smoker	T4N0Mx
CRC_71	Male	56	Nondrinker	Nonsmoker	T4N0Mx
CRC_72	Male	63	Nondrinker	Nonsmoker	T3N2Mx
CRC_73	Male	85	Drinker	Smoker	T3N0Mx
CRC_74	Male	60	Nondrinker	Smoker	T3N0Mx
CRC_75	Male	42	Nondrinker	Nonsmoker	T2N0Mx
CRC_76	Female	85	Drinker	Smoker	T3N0Mx
CRC_77	Male	61	Nondrinker	Nonsmoker	T4N1Mx
CRC_78	Female	67	Drinker	Smoker	T3N1Mx
CRC_79	Male	54	Nondrinker	Nonsmoker	T4N0Mx
CRC_80	Female	76	Drinker	Smoker	T4N0Mx
CRC_81	Female	77	Drinker	Smoker	T3N1Mx

Table S5. Association analyses between individual SNP and CRC risk in the two phases and combined samples

		Phase Ⅰ			Phase Ⅱ			Combined study			
SNP	Genotypes	Cases/ Controls	OR (95% CI) †	*P* ‡	Cases/ Controls	OR (95% CI) †	*P* ‡	Cases/ Controls	OR (95% CI) †	*P* ‡	MAF
rs174575	CC	1,186/1,275	1.00 (Ref)		3,550/6,990	1.00 (Ref)		4,736/8,265	1.00 (Ref)		0.100
	CG	309/234	1.43 (1.18-1.73)	3.24×10^{-4}	886/1,431	1.22 (1.11-1.34)	4.10×10^{-5}	1,195/1,665	1.24 (1.14-1.35)	6.84×10^{-7}	
	GG	29/13	2.24 (1.14-4.38)	1.86×10^{-2}	64/79	1.58 (1.13-2.21)	7.00×10^{-3}	93/92	1.73 (1.29-2.31)	2.41×10^{-4}	
	Dominant		1.43 (1.22-1.77)	7.04×10^{-5}		1.24 (1.13-1.36)	6.08×10^{-6}		1.26 (1.16-1.37)	2.74×10^{-8}	
	Recessive		2.04 (1.04-3.98)	3.68×10^{-2}		1.51 (1.08-2.11)	1.50×10^{-2}		1.64 (1.23-2.19)	8.89×10^{-4}	
	Additive		1.44 (1.21-1.71)	3.16×10^{-5}		1.23 (1.13-1.34)	1.99×10^{-6}		1.26 (1.17-1.36)	2.99×10^{-9}	

Abbreviations: Ref, Reference; OR, odds ratio; CI, confidence interval; MAF, minor allele frequency.

† ORs and 95% CIs calculation were conducted under assumption that variant alleles were risk alleles.

‡ All *P* values were calculated by unconditional logistic regression model after adjusting for gender, age group.